sidering the admitted present state of our knowledge of quality assurance.

It is suggested that the Forward Plan for Health —1977-1981 will have served a most useful purpose if it becomes a stimulus to the private sector health care industry, which is one of the largest and most complex in the United States, to find effective ways to plan *with government* for the future of health care in this nation. This will require (1) that the autonomous and independent organizations, institutions and associations in the private sector find ways to get together for effective short- and long-range planning and (2) that the federal government will be willing to work together with the private sector more as the servant rather than as the master of the people. Whether this can or will be done remains to be seen. The issue is a fundamental one for the survival of the rule of the people by the people in an increasingly complex and interdependent democratic society.

Perhaps there should be some sort of ad hoc coalition of some of the principal organizations and agencies in the private sector to identify health care goals and to see if a coordinated planning effort in the private sector is possible. If this could be done in the Bicentennial year and then coordinated with government planning, health care in this nation could enter a new era in which whatever restrictions and controls there might be would be developed with the system rather than imposed upon it. It is only human nature to work much harder to make one's own plans succeed than someone else's.

—MSMW

Hemolytic Uremic Syndrome

THE HEMOLYTIC UREMIC SYNDROME (HUS) is a clinical entity composed of uremia, hemolytic anemia with characteristically fragmented cells, and usually thrombocytopenia. This syndrome was brought to medical attention in 1955 by Gasser and co-workers.[1] Since then, many cases have been reported with the result that a much broader concept of the syndrome has evolved. In the Specialty Conference appearing in this issue of the JOURNAL, Mendoza uses the case history of a child with HUS primarily to examine in detail the problem of acute renal failure, the prominent clinical challenge in this syndrome. Indeed, it is important that HUS be repeatedly discussed—particularly in California where its occurrence is considered endemic. Since 1963 our group has seen an average of six new cases each year. Because prognosis appears to be influenced by prompt diagnosis and management, physicians in the western United States should know its characteristics.

The HUS has worldwide distribution, particularly in areas with temperate climates. California, Argentina, South Africa and the Netherlands are considered endemic areas. Most cases occur sporadically, although scattered clusters have been reported. Seasonal variation appears to occur in the San Francisco bay area, with the highest incidence in September. There is no sex predilection. The average age of onset is 2 to 5 years. An exception is Argentina where the average age is much younger—13 months; however, even there children as old as 9 years[2] or older[3] have been reported. The syndrome is now being recognized in women, particularly postpartum[4] or after the use of contraceptive pills.[5]

Characteristically, there is a virus-like prodrome, with prominent gastrointestinal symptoms (such as diarrhea, which frequently becomes bloody, and severe abdominal pain). Upper respiratory symptoms may precede these findings. Abdominal pain is recognized more frequently in older children and often leads to misdiagnoses (for example, ulcerative colitis, intussusception and acute appendicitis). On initial examination, the patient is usually pale and edematous; hypertension and hepatomegaly are common. Hemoglobin is low, and levels of blood urea nitrogen are elevated in almost all patients. Leukocytosis, reticulocyte counts greater than 5 percent, and blood and protein in the urine are frequent findings. Thrombocytopenia is present in most cases, the levels of coagulation Factors V, VIII and X are usually not decreased; fibrin split products are more often absent than present. Usually prothrombin time and partial thromboplastin time are prolonged.

As noted by Mendoza, there is no single recognized etiologic agent; rather, several dif-

ferent viruses have been implicated, as well as some bacteria. Epidemiologic studies have shown multiple rising viral titers in family members and other close contacts in whom HUS does not develop. It is unknown why the clinical syndrome develops in some people and not in others. Disappointingly few organisms have been identified, despite extensive investigations.

Although Mendoza presents a different impression, most authorities agree that the pathophysiology of HUS results from accelerated intravascular coagulation. The histologic renal lesions are distinct and characteristic.[6-8] The degree of involvement may vary from minimal thickening of the glomerular capillary wall with prominent mesangeal areas to bilateral cortical necrosis. By light microscopy, the observed abnormalities are quite consistent with lesions of accelerated intravascular coagulation. Electron microscopic findings are unequivocal; electron dense, fibrillar material is observed within the widened radiolucent subendothelial area and between the cytoplasm of endothelial and mesangeal cells. Thrombi, with periodicity characteristic of fibrin, are seen frequently in the capillary lumina. Numerous intact or disintegrating platelets line the glomerular capillary walls. Immunofluoroscopy confirms the deposition of fibrin in the glomerular tufts in tissue examined within the first four to six weeks after onset of the disease. Only rarely has deposition of immunoglobulins been documented. Intravascular thrombosis, *not* restricted to the kidney, is reported in many children dying after prolonged severe azotemia. The histologic lesions are similar to those seen in the generalized Shwartzman phenomenon, and are much more consistent with accelerated intravascular coagulation than are the blood studies.

Mendoza's patient recovered completely, although dialysis was delayed until azotemia was more severe. Our experience at the University of California, San Francisco, indicates that immediate peritoneal dialysis is preferable to delay, and favorably influences the outcome. This position is supported strongly by the findings of Kaplan and co-workers.[9] Dialysis relieves overhydration, restores normal blood pressure (or makes hypertension more easily controlled), averts impending heart failure and permits red blood cell transfusion with less hazard of overloading the circulation. Azotemia and hyperkalemia are alleviated and although the use of digitalis and diuretics may be avoided, administration of aluminum hydroxide and sodium polystyrene sulfonate (Kayexalate®) are usually required for control of elevated serum phosphate and potassium levels. Perhaps permanent damage to the anterior walls can be avoided, if hypertension is prevented early or controlled. As Mendoza points out, 20 to 25 percent of caloric needs are required to minimize catabolism. Concentrated glucose solutions are less sclerosing in larger veins and better nutrition can be maintained if a catheter is placed in the vena cava. Adequate nutrition is important not only to minimize developing azotemia but also to reduce susceptibility to infection.

In all published experience, better symptomatic management has improved the prognosis in HUS. However, mortality or permanent renal insufficiency remain high (between 10 and 20 percent). The findings associated with a poor prognosis are prolonged duration of anuria and initial convulsions. However, there is no initial way to predict duration of anuria nor is it possible to establish the mechanism responsible for the seizure—such as uremia, edema, hyponatremia and thrombosis. Since increased intravascular coagulation is a recognized integral part of this disease and thrombosis is associated with renal necrosis, it is reasonable to use anticoagulant agents as quickly as possible in order to interfere with the process or dissolve the thrombi already present or both. In our series of 73 patients with HUS, 8 of 13 who were anuric for more than six days recovered completely following the use of heparin given intravenously. Only one of seven recovered from a similar duration of anuria treated symptomatically only. Similar experience has been reported by some,[10] while no benefit with administration of heparin has been reported by others.[9] Quite recently there have been a number of reports of favorable outcome following the use of streptokinase,[11] or aspirin or dipyridamole—or both of these.[12]

Since HUS is a common cause of childhood renal failure, a well organized collaboration study is in order, not only to understand the syndrome in more depth but to develop specific therapy.

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Calcium Metabolism

IN THEIR REVIEW, elsewhere in this issue, on calcium and skeletal metabolism, Deftos and his colleagues touch upon many practical issues of interest to clinicians. Of the three hormones concerned with mammalian calcium homeostasis, parathyroid hormone (PTH) and vitamin D may prove to be the two most important. Soon after the independent and nearly simultaneous discovery of calcitonin by Copp[1] and Munson,[2] doubt arose as to whether this hormone plays an important physiological role in adult mammals. Some investigators viewed calcitonin as a vestigial hormone, interesting to investigators but not to clinicians. As highlighted in the review, all of this is changing. Evidence for a physiological role of calcitonin is becoming increasingly convincing, and the importance of calcitonin in diagnosis as well as treatment is now firmly established.

While recent advances in the understanding of vitamin D and calcitonin represent dramatic new insights, abnormal parathyroid function continues to dominate clinicians' thinking. Radioimmunoassays of PTH are at last available and provide an important new diagnostic tool. Properly carried out and interpreted, these assays can provide highly useful information. Poorly carried out or misinterpreted, they lead to confusion. Unfortunately, some commercial laboratories fail to provide clinicians with adequate information concerning the affinity characteristics of the antiserum used. No two antisera are exactly alike. Some possess binding sites predominantly for the intact, 84 amino acid peptide, some predominantly for fragments and some for all immunoreactive forms of circulating PTH. Since the native hormone and fragments possess widely differing biological and kinetic properties, interpretation of assay results depends on what is being measured. The predominant current evidence favors the view that PTH fragments are generated by peripheral metabolism of the native hormone. Metabolism is accomplished by several organs, notably kidney and liver.[3] The biological meaning of metabolism is under study in several laboratories, but at present no conclusive information exists. Metabolism may represent merely catabolic disposal of secreted hormone. Alternatively, it may represent activation.

Increasing application of the radioimmunoassay of PTH in the study of human disease has made it evident that circulating PTH is increased under many circumstances. Nonionic stimulation of PTH secretion has received attention only recently, but enough information is available to suggest that this will prove to be very important. In this regard, Fischer's demonstration that catecholamines stimulate PTH secretion is of particular interest.[4] When a field advances rapidly and questions emerge more rapidly than answers, clinicians would be well-advised to adopt a conservative attitude. Treatment should not be undertaken because of assay results alone, but only when these results seem to be consistent with findings from more traditional assessments of a patient's problems.

This caveat is pertinent particularly to asymptomatic and normocalcemic hyperparathyroidism as discussed in the review. I am ambivalent about the authors' statement that, in an asymptomatic patient, " . . . it is probably prudent to operate in most patients, unless there is contraindication to surgical operation." An asymptomatic patient is likely to have a mild form of hypercalcemic (primary) hyperparathyroidism and is the one in whom finding the abnormal parathyroid gland(s) is difficult. Even expert parathyroid surgeons may find this a vexing problem. Under any circumstances, the need for the services of an expert parathyroid surgeon cannot be overemphasized. It is tragic that surgeons with only a casual acquaintance with the problems of parathyroid surgical procedures continue to embark on this form of operation.

The review does not mention the controversial issue of the indications for preoperative localization of abnormally functioning parathyroid glands.[5,6] There is general agreement that this is indicated in a patient with symptomatic hyperparathyroidism in whom parathyroid surgical operation has previously been unsuccessful. One could make a good argument for preoperative